REMARKS

Claims 1, 16 and 31 have been amended in order to delete the non-elected subject matter. Applicants, of course, reserve the right to file a divisional application on the non-elected subject matter.

Claims 2-15, 19-30, and 32-34, which are directed to the non-elected subject matter of Groups III-XIX, have been cancelled without prejudice to the filing of a divisional application on the same.

Claims 1-31 were in the application as filed. Claims 32-34 were added in the Preliminary Amendment filed on January 9, 2002. Claims 2-15, 19-30, and 32-34 were cancelled by the foregoing amendments. Claims 1, 16-18 and 31 remain in the application.

Claims 1 and 16 are objected to for containing non-elected subject matter. This objection is believed to be overcome and should be withdrawn in view of the above-described amendments to claims 1 and 16 in which the non-elected subject matter has been cancelled.

Claims 17 and 31 are rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,780,466. In support of this rejection, the Examiner has stated that:

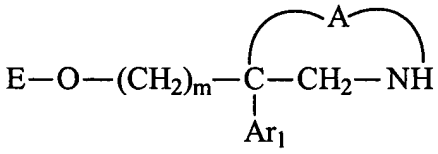
> The prior art of record, U.S. Patent No. 5,780,466 discloses the compounds of formula (II), column 21, line 5 and column 23, lines 30-37 in enantiomerically pure form or in racemic form which are useful in the preparation of the compounds of formula (I), column 2, lines 20-25. The compounds of formula (I) as found in the prior art are useful for therapeutic use in pathological phenomena involving the tachykinin system, such as pain, allergy and inflammation, column 1, lines 14-18. Specific enantiomerically pure compounds of formula (I) of the prior art are found, for example, on columns 116 and 117 in examples 68, 69, and 70. U.S. Patent No. 5,780,466 discloses the compounds of formula (II) of scheme 3, column 33, line 5 wherein E can be H and A is O-CH_2-CH_2, of line 15, column 47 wherein A is O-CH_2-CH2 and E is H, and of preparation 1.5, 2-(3,4-dichlorophenyl)-2-(2-hydroxyethyl)morpholine, which corresponds to applicants instant compound of formula (I) wherein X is chlorine. Column 47, lines 34-43 discloses that to resolve an intermediate of formula (II) one forms a salt with an optically active acid, for example with (+) or (-) tartaric acid.

The difference between the prior art of record and the instantly claimed invention is that the prior art does not specifically disclose the optically active salt of the enantiomerically pure compound of the formula (I) with an optically active acid as instantly claimed. However, the prior art does disclose the compound of formula (II) as found in applicant's instant claims, as formula (I), wherein X is chlorine which can be in the form of an enantiomer or a racemic mixture and can be resolved by formation of a salt with optically active acids, for example with (+) or (-) tartaric acid and discloses the compound of formula (I) in its enantiomerically pure forms, for example, examples 68, 69 and 70, columns 116 and 117.

Minus a showing of unobvious results, it would have been obvious to one of ordinary skill in the art at the time of the invention to prepare an optically active salt of the enantiomerically pure compound of formula (I) wherein X represents a halogen, specifically chlorine, as instantly claimed when faced with the prior art of U. S. Patent No. 5,780,466 which discloses enantiomerically pure compounds of the formula (I), such as those of examples 68-70, and discloses the intermediate compound of formula (II), specifically 2-(3,4-dichlorophenyl)-2-(2-hydroxyethyl)morpholine, which can be resolved by formation of a salt with optically active acids, for example, tartaric acid. The motivation would be to prepare enantiomerically pure compounds of the formula (I) of the prior art by preparing enantiomerically pure compounds of the formula (II) which is done by the formation of a salt with an optically active organic acid, in order to have more compounds of the formula (I) which are useful for the treatment of pathological phenomena involving the tachykinin system.

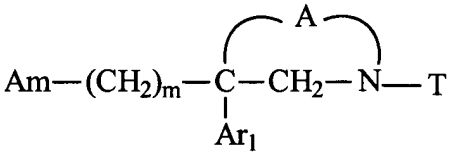
This rejection is traversed and reconsideration and withdrawal thereof are requested for the reasons given hereinbelow.

Emonds-Alt et al., U.S. Patent No. 5,780,466, issued July 14, 1998 disclose compounds of the Formula II



II

which are stated to be useful as intermediates in the preparation of the neurokinin receptor antagonist compounds of the Formula I:



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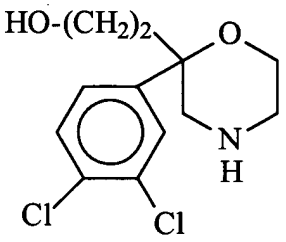
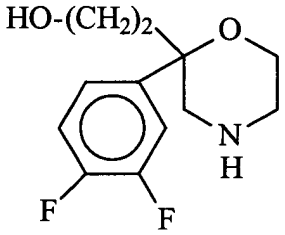
Specifically disclosed as compounds of the Formula II are the compounds of preparations 1.5 and 1.11:

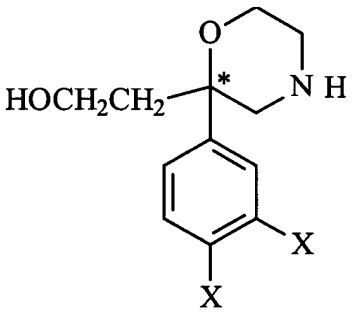


Preparation 1.5



Preparation 1.11

Applicants' instantly claimed compounds, on the other hand, are directed to enantiomerically pure compounds of the Formula I



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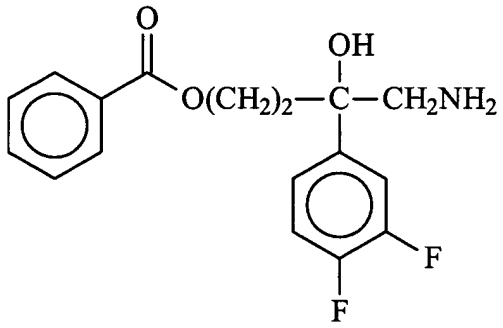
in the form of an optically active salt with an optically active organic acid.

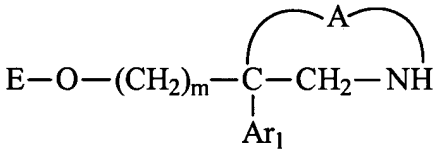
Initially, applicants note that the Examiner appears to be taking the position that it would have been obvious to make the instantly claimed compounds because U.S. Patent No. 5,780,466 discloses enantiomerically pure compounds of the formula I, i.e. examples 68-70, and the intermediate compounds of formula II, specifically 2-(3,4-dichlorophenyl)-2-(2-

hydroxyethyl)morpholine which can be resolved by formation of a salt with optically active acids. In this regard, applicants would point out that the compounds of examples 68-70 of U.S. Patent No. 5,780,466 are in fact not prepared by the resolution of 2-(3,4-dichlorophenyl)-2-(2-hydroxyethyl)morpholine (or any other 2-hydroxyethyl morpholine derivatives of the formula II for that matter) with an optically active acid as has been suggested by the Examiner but rather the compounds of examples 68-70 are prepared by the resolution of a compound of the formula:



i.e., a compound of the formula XXVII, with L-(+)-tartaric acid.

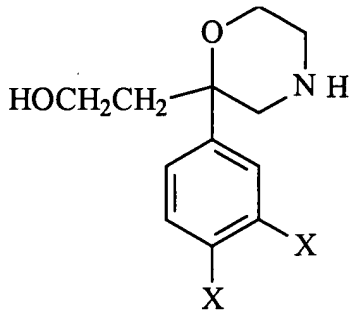
In addition, applicants note that although U.S. Patent No. 5,780,466 has disclosure concerning the compounds of the formula II:



II

in enantiomerically pure form or in racemic form, nowhere in the extensive disclosure of this patent is there any specific disclosure concerning the actual resolution of a compound of formula II, let alone the use of such a compound as an intermediate to prepare enantiomerically pure tachykinin receptor antagonist compounds. Of particular note in this regard is the fact that the groups A and Ar_1 of formula II can represent a vast array of possible substituents and it is not seen how such a vast disclosure could possibly teach or suggest to one of ordinary skill in the art to select out the instant compounds in racemic form let alone in enantiomerically pure form.

This is especially true given the fact that U.S. Patent No. 5,.780,466 actually teaches away from the use of compounds of the formula:



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as intermediates in that it teaches that such compounds are obtained in very low yields of 1% to 2% and, hence, would not be useful as intermediates on an industrial scale (see description on page 2, line 11 to page 4, line 6 of the instant application concerning WO 96/23787, a foreign counterpart of U.S. Patent No. 5,780,466).

In view of the foregoing, applicants submit that U.S. Patent No. 5,780,466 is not competent to render applicants' claimed compounds obvious. Neither this reference, nor any other prior art of which applicants are aware, has any teaching or suggestion which would have led a person of ordinary skill in the art to applicants' claimed compounds. The claimed invention would, therefore, not have been obvious to such a person at the time the invention was made and, hence, the rejection of claims 17 and 31 based on said reference is believed to be unwarranted and should be withdrawn.

Claim 18 is rejected under 35 U.S.C. §103(a) as being unpatentable over U.S. Patent No. 5,780,466 as applied to claims 17 and 31 above and further in view of U.S. Patent No. 5,616,777. In support of this rejection, the Examiner has stated that:

> While U.S. Patent No. 5,780,466 discloses or renders obvious optically active salts of the enantiomerically pure compound of formula (I) wherein X is halogen, specifically chlorine or fluorine, with optically active organic acids as instantly claimed, it fails to disclose the specific optically active organic acids of L-(-) or D-(+)-di-para-toluoyltartaric acid as claimed in claim 18. However, U.S. Patent No. 5,616,777 discloses "chiral acids" which are used to resolve a mixture of diastereomers, with preferences

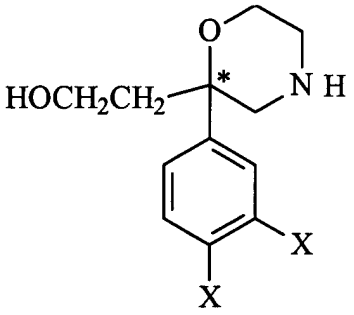
towards L-DTTA (di-p-toluoyl-L-tartaric acid, column 4, line 54) and D-DTTA (di-p-toluoyl-D-tartatric acid, column 4, line 53) (column 5, lines 17-25). Reaction Scheme 1, columns 5 and 6 discloses the use of the "chiral acid" to resolve the diastereomers into salts of the enantiomerically pure compounds with the optically active organic acids or "chiral acids". While U.S. Patent No. 5,616,777 fails to disclose an optically active salt of the enantiomerically pure compound of formula (I) as instantly claimed with an optically active organic acid, it does disclose that L-DTTA and D-DTTA are preferred "chiral acids" which are resolving agents for resolving diastereomers into enantiomerically pure optically active salts with an optically active organic acid.

Therefore, one of ordinary skill in the art, minus a showing of unobvious results, would be motivated to prepare optically active salts of the enantiomerically pure compound of formula (I) with L-DTTA or D-DTTA as instantly claimed when faced with the primary reference which discloses that optically active organic acids such as tartaric acid are resolving agents which prepare optically active salts of the enantiomerically pure compound of formula (II) with optically active organic acids and further in view of the secondary reference which discloses that L-DTTA and D-DTTA are optically active organic compounds which are useful for resolving racemic mixtures, i.e., they are the "chiral acids". Especially since U.S. Patent No. 5,616,777 discloses that L-DTTA and D-DTTA are preferred as the resolving acids, i.e., the "chiral acids" the motivation would be to prepare the enantiomerically pure compounds of the formula (I) as found in U.S. Patent No. 5,770,466, for example, examples 68, 69, 70 etc. which is a useful compound for the treatment of pathological phenomena involving the tachykinin system such as pain, allergy and inflammation (column 1, lines 14-18) by resolving more compounds of the formula (II) as found in U.S. Patent No. 5,780,466 by forming salts with optically active acids, specifically L-DTTA or D-DTTA.

This rejection is traversed and reconsideration and withdrawal thereof are requested for the reasons given hereinbelow.

Initially, applicants would point out that, for the reasons given hereinabove, U.S. Patent No. 5,780,466 is inadequate to either teach of suggest applicants' instantly claimed compounds. Accordingly, the only question which remains is if the secondary reference, U.S. Patent No. 5,616,577, which has been cited by the Examiner, cures the inadequacy of the primary U.S. Patent No. 5,780,466 reference. As pointed out hereinbelow, the secondary reference fails to cure the inadequacy of the primary reference.

U.S. Patent No. 5,616,777, issued April 1, 1997 discloses chiral hydrazine derivatives which are stated to be useful as intermediates in the synthesis of tri-substituted tetrahydrofuran triazole derivatives which are stated to be useful as antifungal agents. Also disclosed is a process for preparing such chiral hydrazines by resolution with chiral acids. Disclosed as preferred chiral acids are L-DBTA, D-DBTA, L-DTTA and D-DTTA. Applicants claimed compounds, on the other hand, are directed to enantiomerically pure compounds of the formula I:



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which compounds differ significantly structurally from the chiral hydrazines disclosed in U.S. Patent No. 5,616,777. Accordingly, it is not seen how the disclosure in U.S. Patent No. 5,616,777 of the use of chiral acids, such as L-DTTA and D-DTTA, to resolve such structurally different chiral hydrazines could possibly teach or suggest to one of ordinary skill in the art applicants instantly claimed compounds in the form of a salt with L-(-) or D-(+)-di-paratoluoyltartaric acid. This is especially so given that, as noted above, the primary reference, U.S. Patent No. 5,780,466, actually teaches away from the use of the instantly claimed compounds as intermediates.

Accordingly, applicants submit that neither U.S. Patent No. 5,780,466 nor U.S. Patent No. 5,616,777 taken alone or in combination are competent to render the subject matter of the instant claim 18 obvious. None of these references, nor any other prior art of which applicants are aware, has any teaching or suggestion which would have led a person of ordinary skill in the art to applicants' claimed compounds. The claimed invention would, therefore, not have been obvious to such a person at the time the invention was made and, hence, the rejection of claim 18 based on said references is believed to be unwarranted and should be withdrawn.

In view of the foregoing amendments and remarks, reconsideration and withdrawal of (a) the objection to claims 1 and 16, (b) the rejection of claims 17 and 31 under 35 U.S.C. §103(a) and (c) the rejection of claim 18 under 35 U.S.C. §103(a) is requested and allowance of claims 1, 16-18 and 31 is respectfully requested.

Respectfully submitted,

Date April 29, 2004

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